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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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(54) Title: A SMALL SYNTHETIC RNA, A METHOD OF PREPARING THE SAME AND USES THEREOF

(57) Abstract: Translation of the hepatitis C virus (HCV) RNA is mediated by the interaction of ribosomes and cellular proteins with an internal ribosome entry site (IRES) located within the 5'untranslated region (5'UTR). We have investigated whether small RNA molecules corresponding to the different stem-loop (SL) domains of the HCV IRES, when introduced in trans, can bind to the cellular proteins and antagonize their binding to the viral IRES, thereby inhibiting HCV IRES-mediated translation. We have found that an RNA molecule corresponding to SL III of the HCV IRES could efficiently inhibit HCV IRES-mediated translation in a dose-dependent manner without affecting cap-dependent translation. The SL III RNA was also found to bind efficiently to most of the cellular proteins which interacted with the HCV 5'UTR. A smaller RNA corresponding to SL e+f of domain III also strongly and selectively inhibited HCV IRES-mediated translation. This RNA molecule showed strong interaction with the ribosomal S5 protein and prevented the recruitment of the 40S ribosomal subunit by the HCV IRES. In conclusion our results demonstrate a novel approach to selectively block HCV RNA translation using a small RNA molecules mimicking the structure of the stem-loop IIIe+f subdomain of the HCV-IRES. The discovery provides a basis for developing a potent antiviral therapy targeting the interaction between the ribosome and the HCV-IRES RNA.

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